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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/472,232	12/27/1999	Jacques Dumas	BAYER-9-C1	8474

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EXAMINER
RAO, DEEPAK R

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/472,232

Applicant(s)

DUMAS ET AL.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-6,9,10,15,16,18-34 and 38-40 ☒ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 25,32-34 and 39 ☒ are allowed.
- 6) ☒ Claim(s) 1,2,4-6,9,10,15,16,18-24,26-31,38 and 40 ☒ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to the amendment filed on December 23, 2004.

Claims 1-2, 4-6, 9-10, 15-16, 18-34 and 38-40 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 15-16, 18-23, 26-29 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of cancer of the colon, does not reasonably provide enablement for the treatment of all other diseases of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant first asserts that 'the specification provides a number of publications that have correlated the inhibition of RAF kinase with the inhibition of the growth of a variety of tumor types'. However, contrary to applicant's assertion, the state of the art references do not establish a therapeutic method for the treatment of all types of diseases mediated by RAF kinase generally. See e.g., Kolch (Nature 1991) provides that RAF-1 inhibitors blocked proliferation of

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specific oncogenes. Monia (Nat. Med. 1996) also provided a role of RAF kinase in the development of specific types of malignancies. None of the state of the art references of record expressed a single therapeutic approach for treating all types of diseases mediated by RAF kinase or cancerous cell growth generally by administering a single class of compounds. Further, the state of the art is not indicative of the fact that treatment of all types of diseases including those of cancerous cell growth or solid cancers mediated by RAF kinase is conventional or well known. The cited references are too speculative. The references are specific with respect to limited types of cancerous growth or malignancy.

Applicant argues that 'no evidence has been presented to refute the findings or conclusions made in the publications'. However, as explained above, the findings and conclusions in the cited publications with respect to inhibition of RAF kinase and the application of such activity for specific types of cancerous growth. Further, it was clearly explained in the previous office action that the claims are drawn to several types of cancers affecting different organs and having different methods of growth or harm to the body, and different vulnerabilities. The development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single therapeutic approach.

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The instant claims recite 'treating a solid cancer, melanoma, or adenoma', however, the art does not identify a single class of compounds that can treat all these types of cancers generally. Further, one skilled in the art of cancer therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse cancers. For example, breast cancer is quite different from liver cancer and even not all breast cancers are identical to each other. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the raf kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to tumor response endpoints. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available and therefore, no chemotherapy is available. This establishes the difficulties involved in the treatment of cancers. The various references of record and those presented at the interview have been considered, however, it is maintained that applicants have not provided sufficient test assays or data to support the method of treatment commensurate in scope with the claims, as of the filing date of the application.

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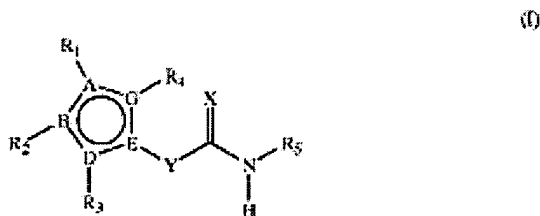
Applicant cites several case laws and argues that the enablement requirement is satisfied. This is not seen to be the case. For example, contrary to what appellants urge by citing *In re Marzocchi*, 169 USPQ 367, the examiner has provided both reasoning including the nature of the invention which is directed to an unpredictable art, citation of case law as well as relevant publication to support the reason for the rejection. Applicant has not identified any state of the art references that clearly establish correlation between the assays employed in the specification and clinical efficacy for the treatment of the claimed diseases. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example *In re Ruskin* 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907.

Applicant cites *In re Brana* and argues that 'it would at most involve routine experimentation for one of ordinary skill in the art to treat any one of the recited cancers with a compound of the invention'. Applicant's reliance on the *Brana* decision is erroneous since the facts were different in more than one respect from the instant case. In *Brana*, the compounds on appeal were of a much narrower scope and there were no method claims. Said compounds were similar in structure to compounds displaying *in vivo* anti-tumor activity based on art-recognized *in vivo* tests and also tested favorably in an *in vivo* test. Thus, contrary to *Brana* it is not evident that at the time of applicant's effective filing that RAF kinase inhibitors having such a diversity of substituents on analogous urea compounds are well known for treating any disease mediated by RAF kinase urged treatable based simply on assay testing relied on herein or for treating solid cancer, adenoma or melanoma generally.

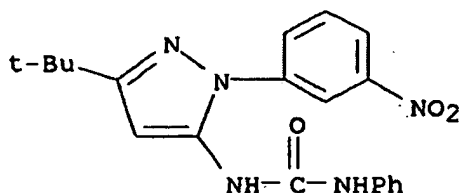
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2. Claims 1-2, 4-6, 9-10, 15-16, 18-24, 26-31, 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Regan et al., U.S. Patent No. 6,080,763. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant cites *In re Jones* to overcome the obviousness rejection. However, *Jones* dealt with the obviousness of a particular claimed ammonium salt based on a generic teaching of "substituted ammonium salts" with no Markush recitation for particular moiety, aminoethoxy ethanol, the salt on appeal. Secondary references applied in *Jones* were deemed not properly combinable with the generic disclosure in the primary reference since the references were not all from the same art area. Unlike the situation in *Jones*, the instantly claimed compounds are expressly taught in a single reference (Regan), which generically discloses all the elements recited in instant claims. In the instant case, the reference generically teaches compounds of structural formula:



and several species wherein the ABDEG ring is a pyrazolyl, see for example, the following species:



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The instantly claimed compounds differ by requiring a substituent $-M-L^1$ on the terminal phenyl group. However, the reference teaches that the phenyl group of R_5 is further substituted with substituents such as alkyl, halo, cyano, alkoxy, phenyloxy, naphthyloxy, etc. and thus, teaches the equivalence of the various substituents. Further, the reference discloses compounds wherein the phenyl (R_5) is substituted by methoxy, cyano, fluoro, etc. and therefore, provides sufficient motivation to one of ordinary skill in the art to prepare compounds using another substituent on the phenyl ring which is taught to be equivalent. Thus, the reference provides sufficient motivation for the ordinary artisan to modify the reference compounds to arrive at the instantly claimed compounds because one of ordinary skill in the art only needs to make one change to the reference disclosed compound to arrive at the instantly claimed compound.

Applicant argues that the reference compounds are described to be 'useful for treating diseases and pathological conditions involving inflammation and there is no suggestion that the compounds are useful in treating raf mediated diseases'. The instant claim 15 recites 'method for the treatment of disease mediated by raf kinase' and the specification discloses that such diseases include tumors and cancerous cell growth (see page 2). Analogously, the reference also discloses that the reference compounds have therapeutic effect on various diseases of mammal through the inhibitory activity on variety of inflammatory cytokines such as IL-1, $IFN\gamma$, etc. which diseases include oncological diseases (see col. 3); multiple myeloma (see col. 5), etc. The reference also indicates that 'cytokines stimulate proliferation' and the compounds of the invention inhibit the release of cytokines. Further, the reference teaches that $IFN\gamma$ is implicated in a number of diseases, including cancers, and cancers generally include any proliferation of cells, which results in unregulated growth.

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Allowable Subject Matter

Claims 33-34, 25, 39 and 32 are allowed. The closest reference of record, US'763 does not teach or fairly suggest the instantly claimed compounds.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-

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0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

April 1, 2005